

In re Application of
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II. REMARKS

Claims 8 to 17 are pending. A marked-up copy showing the amendments to the Title and the claim is attached hereto as Exhibit A.

A. Regarding the Amendments

The Title of the application has been amended to reflect the subject matter claimed as the invention. As such, the amendment merely addresses a formality, and does not add new matter.

Claim 8 has been amended to more clearly indicate a result of the claimed method. The amendment is supported by the preamble to the claim and, therefore, does not add new matter.

B. Rejections under 35 U.S.C. § 112

The objection to the specification and corresponding rejection of claim 10 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement are respectfully traversed.

Claim 10 is directed to a method of ameliorating AIDS, an autoimmune disease, or graft rejection by administering to a patient an antibody as defined. It is stated in the Office Action that the specification does not provide sufficient guidance for one skilled in the art to treat such disorder, and that general protocols for effective antibody-based treatment of the recited disorders are not established in the art.

Applicant submits, however, that a method of the invention is a passive immunization method, which comprises administration of an antibody, and that methods of passive immunization are well known in the art. For example, administration of anti-venins, which are antibodies specific for particular toxins such as snake or bee venoms, has long been used and is routine in the art. Furthermore, the specification discloses routes of administration and a range of dosages of an antibody that can be administered, and also acknowledges that a dosage can be adjusted based on a counter-indication observed due to the administration (see, for example, page 17, line 15, to page 18, line 9).

It is also stated in the Office Action that obstacles associated with therapeutic approaches to HIV-1 infection are well documented in the art, including, for example, the fact that viral transmission can occur via passage of the virus from mononuclear cells to other cells or via infection with free virus. In addition, the Fahey et al. reference, which indicates that administration of an anti-gp160 antibody did not achieve a clinical benefit in HIV infected individuals (Table 1), is cited as evidence that the skilled artisan would not reasonably have believed that antibody based therapies would be useful for treating a disorder such as AIDS.

Applicant points out, however, that Fahey et al. state that "80% or more of HIV⁺ individuals have antibodies capable of blocking gp160 binding to CD4 T cells *in vitro*. Thus, it is not clear how adding these additional antibodies would make a difference." (Fahey et al., page 3, right column, third paragraph). As such, it is unclear from Fahey et al. whether one skilled in the art would have expected administration of the anti-gp160 antibodies to have any effect in an HIV infected individual because it was already known that the vast majority of such individuals naturally expressed such antibodies.

Furthermore, the method described by Fahey et al. is distinguishable from the present methods because Fahey et al. teach that gp160 is an immunosuppressive agent and the anti-gp160 antibodies were administered with the hope that they would result in the removal or reduction of gp160, thereby allowing for an improved B cell response (see Fahey et al., page 3, right column, third paragraph). In contrast, the antibodies useful in a method of the invention suppress intercellular leukocyte adhesion (see, for example, page 5, lines 13-16) and, therefore, can prevent an immune response, for example, by suppressing interactions among leukocytes, including T cells and B cells, which express the LAR, LFA-1 (see page 3, lines 1-5). Further in this respect, and specifically with respect to HIV infected cells, the specification discloses that an antibody useful in a method of the invention prevents syncytium formation between HIV infected

T cells and uninfected T cells (see page 21, lines 11-20; page 24, lines 5-13). It is submitted that, in view of these results, one skilled in the art, viewing the specification, would have known that an antibody useful in a method of the invention can decrease the spread of HIV in T cells of an individual by suppressing adhesion of an HIV infected T cell with an uninfected T cell, thereby ameliorating the immune response disorder.

In summary, the specification discloses dosages and routes of administration of an antibody specific for a LAR β chain and further discloses use of such antibodies to ameliorate an immune response disorder characterized, at least in part, by leukocytes expressing an LAR β chain. In addition, the specification exemplifies such suppression of intercellular leukocyte adhesion by demonstrating that the antibodies can prevent syncytium formation of HIV infected T cells and uninfected T cells, such that the skilled artisan would have known that a method of the invention can be useful for slowing the spread of HIV infection in an individual. As such, it is submitted that, in view of the specification, as well as knowledge in the art of passive immunization methods, it would not have required undue experimentation for one skilled in the clinical arts to practice a method of the invention. Accordingly, it is respectfully requested that the objection to the specification be withdrawn, and that the corresponding rejection of claim 10 under 35 U.S.C. § 112, first paragraph, be removed.

C. Prior Art Rejections

The rejection of claims 8, 9, 11 and 13 to 15 under 35 U.S.C. § 102(e) as allegedly anticipated by Arfors is respectfully traversed.

The claims are directed to a method of ameliorating an immune response mediated disorder in an animal by administering, in an amount capable of suppressing intercellular leukocyte adhesion, an antibody that binds an epitope on a leukocyte adhesion receptor (LAR) β chain. Arfors describes the use of an antibody (Mab 60.3) to prevent leukocyte mediated tissue

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damage that occurs during tissue ischemia/reperfusion (see, for example, Abstract; column 1, lines 5-12; and column 2, lines 50-55). Specifically, Arfors recognizes that tissue damage due to ischemia/reperfusion is due to reactive oxygen generated by polymorphonuclear (PMNs) leukocytes (column 1, lines 28-54), and describes the use of antibodies specific for polypeptide components of the leukocyte adhesion complex (LAC), including, for example, LFA-1 and Mac-1, as a means to prevent adhesion of PMNs to endothelial cells (column 2, lines 57-63). As such, a method of Arfors provides a means to prevent the generation of reactive oxygen species in a tissue subject to ischemia/reperfusion.

Arfors does not teach or suggest immune response mediated disorders or a method of ameliorating an immune response mediated disorder, and does not teach or suggest that anti-LAC antibodies such as Mab 60.3 can be used to ameliorate an immune response mediated disorder. As such, it is submitted that the reference cannot anticipate the claimed methods and, therefore, is respectfully requested that the rejection of claims 8, 9, 11 and 13 to 15 as anticipated by Arfors be removed.

The rejection of claim 8 under 35 U.S.C. § 102(b) as allegedly anticipated by Vedder et al. is respectfully traversed.

Applicant points out that the authors of the Vedder et al. reference include Arfors (see above). Vedder et al. (like Arfors) describe the use of an antibody (Mab 60.3) to prevent leukocyte adhesion to endothelium and, therefore, leukocyte mediated tissue damage that occurs during tissue ischemia/reperfusion (see Abstract; page 941, first paragraph of "Discussion" to page 943, left column, second paragraph). Thus, Vedder et al. (like Arfors) describe preventing ischemia/reperfusion tissue damage that is caused due to the release of proteases, toxic oxygen metabolites, and vasoactive substances by neutrophils, but do not teach or suggest an immune response mediated disorder, or a method of ameliorating an immune response mediated disorder.

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As such, it is submitted that the reference cannot anticipate the claimed methods and, therefore, is respectfully requested that the rejection of claim 8 as anticipated by Vedder et al. be removed.

The rejection of claims 8, 9, 11 and 13 to 15 under 35 U.S.C. § 103(a) as allegedly obvious over Arfors, or Vedder et al., in view of Springer et al., is respectfully traversed.

The Arfors and Vedder et al. references are applied as describing anti-CD18 monoclonal antibodies (e.g., Mab 60.3) that inhibit leukocyte adherence functions and inhibit ischemia/reperfusion injury, and as speculating that the findings may be relevant to many disorders that result from ischemia and reperfusion, including organ transplantation. The Springer et al. reference is applied as describing administration of LFA-1 or proteins capable of competing for receptors and of inhibiting cell to cell binding, and as recognizing the potential applicability of such compositions for treating autoimmune diseases and graft rejection. It is alleged in the Office Action that it would have been *prima facie* obvious to combine the teachings of the references to administer an anti-CD18 antibody such as Mab 60.3, which was shown to inhibit cell adhesion, to treat an autoimmune disease or graft rejection, the motivation to combine the references being provided by "the teachings of Springer et al. and Vedder et al. as previously characterized" (OA, page 6, third paragraph).

It appears from the Office Action that the motivation to combine the references is provided by the mention of organ transplantation by Vedder et al. Applicant submits, however, that one of ordinary skill in the art would not have been motivated to combine Arfors and/or Vedder et al. with Springer et al. because Arfors and Vedder et al. describe methods relating to the use of antibodies to prevent ischemia/reperfusion injury, including that occurring as a result of organ transplantation, whereas Springer et al. describe methods relating to the use of proteins (but not antibodies) for treating an immune disorder such as allograft rejections. More specifically, Vedder et al. state "The organ injury that results from ischemia and reperfusion determines the outcome of ... organ transplantation...." (page 939, first paragraph of

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"Introduction"). As such, it is clear that Vedder et al. are not referring to an immunologic based rejection of an organ transplant (Cf. Springer et al., page 12) but, instead, are describing injury that can occur upon reperfusion of the transplanted organ. In contrast, Springer et al. describe graft rejection due to an immune response, but do not teach or suggest ischemia/reperfusion.

Furthermore, Arfors and Vedder et al. describe the use of an anti-LAC antibody to prevent leukocyte binding to endothelium. In contrast, Springer et al., while generally describing antibodies specific for LAC components and the use of such antibodies for diagnostic purposes, does not teach or suggest the use of such antibodies to ameliorate an immune response mediated disorder. Instead, Springer et al. describe the use of the polypeptide components of LAC (e.g., LFA-1), including peptides thereof, to treat an immune disorder (see page 12).

For the above reasons, it is submitted that there is nothing in the Arfors reference or the Vedder et al. reference, which describe the use of antibodies to prevent ischemia/reperfusion injury, that would have motivated one of ordinary skill in the art to combine one or both references with the Springer et al. reference, which describes the use of polypeptides or peptide fragments thereof to treat an immune disorder. Accordingly, it is respectfully requested that the rejection of claims 8, 9, 11 and 13 to 15 as obvious over Arfors, or Vedder et al., in view of Springer et al. be removed.

The rejection of claims 11 and 12 under 35 U.S.C. § 103(a) as allegedly obvious over Arfors, or Vedder et al., in view of Springer et al., and further in view of Hildreth et al., is respectfully traversed.

The Arfors, Vedder et al., and Springer et al. references are applied as discussed above. Hildreth et al. is provided as describing antibody H52, which corresponds to the antibody produced by hybridoma cell line ATCC HB X, as recited in the claims. It is alleged in the Office Action that it would have been *prima facie* obvious to substitute H52 into the methods suggested by the combined teachings of the Arfors, Vedder et al., and Springer et al. because Hildreth et al.

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teaches that Mab H52 had been shown to inhibit all T cell functions tested in a manner similar to Mab 60.3, which was shown to be effective for inhibiting ischemia/reperfusion injury.

For the reasons set forth above, however, it is submitted that one of ordinary skill in the art would not have been motivated to combine Arfors and/or Vedder et al. with Springer et al. because the references are directed to different disorders, i.e., ischemia\reperfusion injury as compared to immune disorders, respectively, as well as to different compositions for treating the disorders, i.e., antibodies as compared to LAC polypeptides or peptide portions thereof, respectively. Applicant further submits that there is nothing in the Hildreth et al. reference that would have motivated the artisan to combine Arfors and/or Vedder et al. with Springer et al. or with the Hildreth et al. reference. In this respect, it is stated in the Office Action that motivation to combine the references is based on "the teaching of Hildreth et al. that Mab H52 had been shown to inhibit all T cell functions tested in a manner similar to Mab 60.3" (OA, page 7, first paragraph). However, it is not apparent from a review of the Hildreth et al., Arfors, and Vedder et al. references which T cell functions of H52 were tested in a manner similar to Mab 60.3. For example, Arfors describes the ability of Mab 60.3 to reduce neutrophil adherence *in vitro* and that prevention of neutrophil adherence by the antibody *in vivo* significantly attenuated increased vascular permeability due to ischemia/reperfusion (column 7, lines 3-15). Arfors also indicates that Mab 60.3 inhibits leukocyte adherence to endothelial cells *in vitro* and *in vivo* (column 2, lines 24-28). However, Arfors does not appear to discuss T cell functions. Vedder et al. describe the effect of Mab 60.3 on vascular permeability *in vivo* and attribute the effect to leukocytes. Vedder et al. discuss that ischemia/reperfusion injury can be due, for example, to reactive oxygen species, but do not appear to discuss any effect of Mab 60.3 on T cell functions. As such, it is submitted that there is nothing in the Arfors reference or the Vedder et al. reference that would have motivated one skilled in the art to combine either or both of the references with the Hildreth et al. reference or, for the reasons discussed above, with the Springer et al. reference. Accordingly, it is respectfully requested that the rejection of claims 10 and 11 as obvious over

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Arfors, or Vedder et al., in view of Springer et al., and further in view of Hildreth et al., be removed.

The rejection of claims 16 and 17 under 35 U.S.C. § 103(a) as allegedly obvious over Arfors, or Vedder et al., in view of Springer et al., and further in view of Pastan et al., is respectfully traversed.

The Arfors, Vedder et al., and Springer et al. references are applied as discussed above. Pastan et al. is provided as describing the concept of using immunotoxins for treating an autoimmune disease, or in autologous bone marrow transplantation and to improve organ graft survival. It is alleged in the Office Action that it would have been *prima facie* obvious to combine the teachings of the cited references to produce conjugates comprising anti-LAR- β chain specific monoclonal antibodies and cytotoxic moieties, and to use such conjugates to treat an autoimmune disease.

For the reasons set forth above, however, it is submitted that one of ordinary skill in the art would not have been motivated to combine Arfors and/or Vedder et al. with Springer et al. because the references are directed to different disorders, i.e., ischemia\reperfusion injury as compared to immune disorders. Applicant further submits that there is nothing in the Pastan et al. reference that would have motivated the artisan to combine Arfors and/or Vedder et al. with Springer et al. As such, Pastan et al. do not provide that which is missing in the previously cited references and, therefore, it is respectfully requested that the rejection of claims 16 and 17 as obvious over Arfors, or Vedder et al., in view of Springer et al., and further in view of Pastan et al., be removed.

D. Double Patenting Rejection

Claims 8 to 17 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1 to 7 of U.S. Patent No. 5,888,508.

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Applicant acknowledges the rejection and will file a Terminal Disclaimer, disclaiming any term of a patent issuing from the subject application that may extend beyond the term of U.S. Patent No. 5,888,508, upon receiving an indication that the present claims otherwise are in condition for allowance.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect respectfully is requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,


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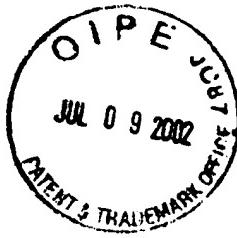
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Enclosure: Exhibit A

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COPY OF PAPERS
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EXHIBIT A

MARKED VERSION OF TITLE AND CLAIMS SHOWING THE AMENDMENTS

The Title was amended as follows:

**METHOD OF USING MONOCLONAL ANTIBODIES AGAINST LEUKOCYTE
ADHESION RECEPTOR β-CHAIN[, METHODS OF PRODUCING THESE ANTIBODIES
AND USE THEREFORE]**

Claim 8 was amended as follows:

8. (Amended) A method of ameliorating an immune response mediated disorder in an animal, the method comprising [which comprises:] administering to the animal a therapeutically effective amount of an antibody, capable of suppressing intercellular leukocyte adhesion, wherein the antibody binds to an epitope on the leukocyte adhesion receptor β-chain, thereby ameliorating the immune response disorder in the patient.